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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,349	04/15/2005	Catherine J. Pachuk	NUCL-019/01US 306512-2117	9095
58349 7590 04/08/2008 COOLEY GODWARD KRONISH LLP ATTN: Patent Group Suite 1100 777 - 6th Street, NW WASHINGTON, DC 20001				
EXAMINER				
SCHNIZER, RICHARD A				
ART UNIT		PAPER NUMBER		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/531,349

Applicant(s)

PACHUK ET AL.

Examiner

Richard Schnizer, Ph. D.

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 March 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 108-174 is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 108-129, 135-138, 142, 146, 147, 150-158, 161-168, 173 and 174 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 April 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-846)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

Continuation of Disposition of Claims: Claims **withdrawn** from consideration are 130-134, 139-141, 143-145, 148, 149, 159, 160 and 169-172.

DETAILED ACTION

An amendment was received on 3/3/08. Applicant elected without traverse group 1, and the species of construct encoding an RNA molecule, or an RNA molecule, having at least two double-stranded segments with substantial identity to at least two target polynucleotide sequences of a virus, wherein the RNA molecule comprises one or more stem-loop structures comprising a double-stranded stem region and a single-stranded loop region, each stem loop structure being separated by a single-stranded spacer region, wherein the RNA molecule comprises a plurality of RNA molecules covalently linked in a 5' to 3' orientation, and wherein the construct lacks a gene encoding an RNA polymerase.

Applicant indicates that claims 108-129, 135-138, 142, 146-148, 150-158, 161-168, 173, and 174 read on the elected species. However, claim 148, drawn to an expression construct encoding an RNA complex or molecule comprising double stranded segments having substantial identity to a gene from two or more pathogens does not read on the elected species. The elected species allows only for double-stranded segments with substantial identity to at least two target polynucleotide sequences of a virus, not more than one virus.

Claims 130-134, 139-141, 143-145, 148, 149, 159, 160, and 169-172, are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/3/08.

Claims 108-129, 135-138, 142, 146, 147, 150-158, 161-168, 173, and 174 are under consideration in this Action.

Comment

The specification contains the phrase "Use of Double-Stranded RNA for Identifying Nucleic Acid Sequences that Modulate the Function of a Cell", filed July 31, 2003, and PCT/US03". and at page 116, the phrase "Double-stranded RNA Structures and Constructs and Methods for Generating and Using the Same", C. Satishchandran, Catherine Pachuk, David Shuey, Maninder Chopra, and PCT/US03"

It appears there is sufficient information in these phrases for Applicant to file an amendment filling in the rest of the PCT Application Nos. without adding new matter.

Specification

The specification is objected to. The status of Application Serial Nos. 10/425,006, cited at page 52, line 26, page 73, line 30, page 141, line 3; page 153, line 28, and 10/062707, cited at page 72, lines 6 and 11, and page 150, line 29, should be updated (abandoned).

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **The specification at page 83, lines 5-15, page 84, lines 2-11, page 107, top and lines 12-14, and pages 109, 110, 112, 113, 119-121, 126, 147, and 148, discloses nucleotide sequences in excess of 9 bases, but there is no Sequence Listing in the instant application.** Applicant must provide:

An initial computer readable form (CRF) copy of the "Sequence Listing".

An initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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For questions regarding compliance to these requirements, please contact:

- For Rules Interpretation, call (571) 272-0951

• For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 or directly at 703-305-3028 / 703-308-6845 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.

• Send e-mail correspondence for Patentin Software Program Help @ ebc@uspto.gov.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 115 and 162 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 115 is indefinite in its recitation of "a Bernie Moss (BM) hairpin." The specification indicates at paragraph 101 that a BM hairpin is "a hairpin structure as described in, e.g., Fuerst and Moss, "Structure and stability of mRNA synthesized by vaccinia virus-encoded bacteriophage T7 RNA Polymerase in mammalian cells", J. Mol. Biol. 206:333-348, 1989. The presence of a BM hairpin at the 5' terminus of an RNA transcript stabilizes the proximate transcript region and protects the 5' terminus of the transcript from degradation and/or loss due to staggered initiation of transcription." It is not clear from this definition what are the particular structural characteristics of a Bernie Moss hairpin, so the term is considered to be indefinite. For the purpose of examination, the phrase BM hairpin is interpreted to embrace any hairpin, because any

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terminal hairpin would reasonably be expected to protect from degradation the terminus of a transcript at which it was located.

Claim 162 recites "the polynucleotide sequence" without proper antecedent basis. The antecedent for "the polynucleotide sequence" in claim 108, is the target polynucleotide. However, claim 162 implies that "the polynucleotide sequence" must be the RNA molecule or in the construct encoding it. The claim is ambiguous.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 115 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 115 requires a "Bernie Moss hairpin", but the specification fails to define this term except by reference to non-patent literature. In any application that is to issue as a U.S. patent, essential material may only be incorporated by reference to a U.S. patent or patent application publication. See MPEP 608.01(p), and 37 CFR 1.57. Because the term "Bernie Moss hairpin" is claimed, it is essential material that is necessary to provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

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connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C.

112. Because "Bernie Moss hairpin" is not a term of art (0 hits in Medline, 1 hit in the US Patent database, i.e. this application), the specification must provide an adequate definition. Such a definition may not be made by incorporation by reference to a non-patent publication. Accordingly, the failure to define in the specification or by proper incorporation by reference the term "Bernie Moss hairpin" results in a failure to satisfy the enablement requirement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 108-129, 135-138, 142, 146, 147, 150-158, 161, 163-168, 173, and 174 are rejected under 35 U.S.C. 102(e) as being anticipated by Turner et al (US 20040053876).

Turner taught expression constructs encoding multiplex hairpin siRNAs comprising several hairpin structures joined by single stranded linkers of 1 to 3 or more

nucleotides. The hairpins function as siRNAs after cleavage of the single stranded regions and release of the hairpin siRNAs from the multiplex. Each hairpin comprises first and second strands wherein the first strand of the hairpin was complementary to a target RNA, and the second strand of the hairpin was complementary to the first. Turner explicitly contemplates multiplex hairpin siRNAs comprising at least 3 hairpins separated by unpaired linkers. See e.g. paragraphs 221 and 234. The duplex regions of the individual hairpins may be interrupted by one or more mismatches. See paragraphs 9 and 121.

Turner also taught RNAs comprising non-overlapping antisense sequences that are organized as a hairpin comprising base-paired sense and antisense segments, separated by mismatch regions giving rise to unpaired "bubbles" that allow processing to release siRNAs from the RNA. See paragraphs 204, 211, and 218.

Turner also taught DNA expression constructs for the RNAs, wherein the expression constructs comprised more than one promoter. See e.g. claim 21.

The first and second strand of the hairpins can be joined by a loop comprising about 3-10 nucleotides. See paragraph 166.

In constructs comprising two or more hairpins, the 5'-most and 3'-most hairpins are considered to be Bernie Moss hairpins. These constructs also meet the limitations of instant claim 129.

Pertinent to claims 117-121, the hairpin siRNAs can be directed against different regions of the same target gene, such as a viral gene, and can be directed against

multiple different target viral genes (RNAs) (see paragraphs 116, 222, 227, 265, 292, 295, and 318.

The double stranded regions of the hairpins are 18-29 nucleotides in length. See paragraph 9.

The hairpin siRNA can comprise 5'- and/or 3-overhangs.

The target sequences may be in human cells. See paragraphs 16-23

The construct may be a plasmid, see paragraphs 238, 239, 241, 327, and 328.
RNA pol I, II, or III promoters may be used. See paragraphs 147, 157, and 224.

Pertinent to instant claim 163, the siRNA expression construct can comprise flanking sequences such as those in Fig. 14B of Turner. Note that hairpin siRNAs are inserted into the underlined BbsI cloning site. The sequences upstream and downstream of the cloning site each comprise more than four guanosines.

The vector may be formulated in a physiologically acceptable excipient such as a lipid. See paragraphs 152 and 275.

The teachings relied upon for this rejection are supported by one or more of priority documents 60/367587, filed March 26, 2002; 60/381766, filed May 20, 2002; 60/403122, filed August 13, 2002.

The following rejection is not directed to the elected species, but is made against the generic invention as a courtesy to Applicant to demonstrate the breadth of the claims as written, and to further demonstrate that the generic claims are not allowable.

Claims 108-115, 122, 125-128, 129?, 135-138, 142, 154-156, 161, 164-168, 173, and 174 are rejected under 35 U.S.C. 102(b) as being anticipated by Masson et al (Proc. Nat. Acad. Sci. USA 84: 6815-6819, 1987).

Masson taught yeast expression vectors encoding a gene for a synthetic suppressor tRNA^{phe}. The gene encoded a precursor tRNA of the general structure set forth in Fig. 1 on page 6815 (see "Oligonucleotides and Gene Synthesis" on page 6816).

The structure of the encoded tRNA precursor meets the limitations of the recited "RNA complex" for the following reasons. It comprises a first strand and a second strand that hybridize under physiological conditions to form a double stranded region. The ds region can be considered to comprise one or more mismatched regions that separate the ds region into two or more ds segments. Such mismatched regions can be considered to be the 2-2 dimethyl G immediately 3' of the D-loop, the loop immediately 3' of the anticodon, the unpaired loop in the intron (in the anticodon stem), or the variable arm (containing 7-methyl G). Cleavage by a single stranded nuclease in any of these unpaired regions would give rise to two RNA molecules each comprising at least one ds region. The entire tRNA has homology to a "target polynucleotide sequence" i.e. the tRNA gene. The term "target" is interpreted broadly here to include sequences that could be a target for hybridization.

The structure of the encoded tRNA precursor meets the limitations of the recited "RNA molecule" for the following reasons. It comprises a stem loop structure separated by single strand spacers, e.g. the acceptor arm and the anticodon stem can be

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considered to be a ds stem that is interrupted by regions comprising unpaired bases (e.g. the variable arm) as well as the ψ -loop on one strand and the D-loop on the other, opposite strand.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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/Richard Schnizer, Ph. D./
Primary Examiner, Art Unit 1635